REMARKS

In this response to the Office Action mailed October 21, 2003 (Paper No. 14), the Examiner objected to claims 75-101 because the claims were dependent on canceled claims. The Applicants have added and amended the claims to better characterize the invention and to correct dependencies. As such, the pending claims are now claims 62-127. Support for the additional claims and claim amendments are discussed below.

The Examiner objected to the specification because it failed to include proper headings of the subsections of the specification as generally required. Applicants have amended the specification where indicated to include proper headings including brief descriptions of the drawings. Support for the drawing descriptions can be found in the specification at page 40 lines 12 to 13, page 41 lines 2 to 10, and page 43 lines 16 to 27. No new matter has been added by amendment.

Rejection under 35 U.S.C.§112, first paragraph

The Examiner rejected claims 62-101 under 35 U.S.C.§112, first paragraph as failing to comply with the written description requirement. The Examiner states that the conditions of claim 62, in the last paragraph of the claim, of the different pore sizes provided by the different conditions are not readily apparent in the specification and that the pages and lines in the specification where these pore sizes and conditions are recited should be pointed out. The Examiner also stated that the conditions of dependent claims 64-74, 76-93 and 95-101 are not readily apparent in the specification and that the pages and lines in the specification where these conditions are recited should be pointed out.

Applicants have amended claims 64-74, 76-93 and 95-101 to clarify the claimed subject matter and additionally, herein provide the following support for the claims rejected.

Claim 62 is amended indicating clear and positive process steps and how each of the different process conditions are used in the process. In particular Basic pores of sizes up to 0.5 μm are created using very high emulsion deformation rate flows in which the flow is predominantly extensional and at a low emulsification temperature. Support can be found on page 20, line 1- page 21, line 3. Basic pores in the range of 50 – 300 μm are created using high emulsification temperatures (about 60 C or greater) and a deformation rate which is just above the critical deformation rate, below which the emulsion becomes unstable. Support for this can be found on: page 20, line 22 – page 21, line 2; page 22, line 16 – page 23, line 23; and example A1. For coalescence pores, support can be found on: page 10, line 23 – page 11, line 4; page 21, line 4 – page 22, line 18; and examples A2 and A6. Nano pores of nano-pore size up to 100 nm are obtained by adding a filler in the oil phase of a Basic pore emulsion and removing by solvent extraction after polymerization. Support can be found on page 11, line 22 – page 12, line 19; page 23, line 25 – page 24, line 19; and example A6.

Claim 63 is amended to an independent claim which defines an alternative limitation of the process of claim 62, taking support as shown in the enclosed, again indicating clear and positive process steps (line 1 – 12) and how each of the different process conditions are used in the process.

Claims 64 to 74 are amended to indicate where the conditions of the claims are inserted in the process of Claims 62 and 63, and support is indicated above as well as in the following:

Claims 64 – 69**:** These claims recite methods for obtaining different types of pore structures as well as bringing together different types of structures in one 'In vitro organ module'. Support of obtaining such structures has been already cited above. Support of formation of 'in vitro organ support module' is described in page 7, lines 16-27; page 8, lines 1-13; page 9, lines 10-28; page 12, lines 15-24; page 14, lines 20-24; pages 16,17 (all); page 18, lines 17-23; and example C;

Claims 70- 71: These claims recite temperature conditions to control Basic pores. Support can be found at page 22, lines 12-27; page 23, lines 1-2; and example A1.

Claims 72-74: These claims recite the use of additional components in the oil and aqueous phases in coating, Coalescence pores, and the control of interconnect size. Support can be found at page 10, lines 16-24; page 11, lines 14-28; page 12, lines 1-10 and 26-29; page 13, lines 1-8; page 23, lines 23-28; and examples A2, A3, A4, and A5.

Claims 76-93: These claims recite the formation of micro-capillary structures and multi-pore size materials for in vitro organ support. Support can be found for the amended claims as follows:

Claim 76: page 4, line 26;
Claim 77: page 10, line 27 and page 40, line 15 and page 5, line 5;
Claim 78: page 18, line 13;
Claim 79: page 44, line 2;
Claim 80: page 11, lines 14 to 15, page 23, line 27, and page 12, lines 3-4;
Claim 81: original claim 2 and page 5, lines 22 – 25;
Claim 82: original claim 3 and page 6, lines 10 – 13;
Claim 83: original claim 4 and page 14, lines 4 – 18, page 6, lines 13 – 14;
Claim 84: original claim 5 and page 7, line 25 – page 8, line 8;
Claim 85: original claim 6 and page 9, lines 15 – 16;
Claim 86: original claim 7 and page 17, lines 14 - 15 and page 18, line 13;
Claim 87: original claim 8 and page 9, lines 23 – 25;
Claim 88: page 9, lines 26 – 28;
Claim 89: original claim 10 and page 12, lines 12 – 13;
Claim 90: original claim 11 and page 12, line 26 – page 13, line 5;
Claim 91: original claim 12 and page 9, lines 1 – 5;
Claim 92: original claim 13 and page 13, lines 18 – 24;
Claim 93: original claim 14 and page 13, line 26 – page 14, line 2; and
Claim 94: original claim 19 and page 15, lines 1 – 2 and page 5, line 22.

Claims 95-101, and 105-107: These claims relate to the application of the invention to the field of tissue engineering. Support can be found for the amended claims as follows:

Claim 95: original claim 19 and page 15, lines 4 – 9;
Claim 96: original claim 19 and page 15, line 5;
Claim 97: original claim 19 and page 15, line 6;
Claim 98: original claim 20 and page 15, lines 20 – 24;
Claim 99: original claim 21 and page 5, line 10, and page 16, lines 2 – 4;
Claim 100: original claim 24 and page 6, lines 19 –21; and
Claim 101: page 5, lines 8 – 14 and page 16, lines 5 – 6;
Claim 105: original claim 22 and page 16, lines 9 – 13;
Claim 106: page 12, lines 15 – 17 and page 6, lines 8 – 14; and
Claim 107: original claim 90 and page 3, lines 5 – 8.

Claim 102 is a new dependent claim carved out of original claim 62. Support can be found on page 11, lines 6 – 20; page 15, line 4 – page 19, line 25; and example C.

Claims 108 – 123 depend from new independent claim 104 which is derived from claim 62 and 63 and page 11, lines 2 – 8 of the specification, and are supported in the specification in the same manner as claims 76-94 above.

Claims 124 – 127 depend from amended independent claim 63 and find support in the specification at original claim 22 and page 16, lines 9 – 13; page 12, lines 15 – 17 and page 6 line 8 – 1; claim 90 and page 3, lines 5 – 8.

In response to the Examiner's rejection Applicants have amended the claims and identified support for the rejected claims within the specification and claims as originally filed. As such, Applicants respectfully request that the Examiner withdraw the rejection in view of Applicants' response.

<u>Rejection under 35 U.S.C. §112, second paragraph</u>

The Examiner rejected claims 62-104 under 35 U.S.C. §112, second paragraph, as being indefinite for failing to point out and distinctly claim the subject matter which Applicants regard as the invention.

The Examiner stated that the claims are confusing due to the language at the top of page 2 of Applicants' previous amendment requiring six different alternative processes requiring different steps and conditions to obtain different pore sizes. Applicants have amended claim 62 to more clearly define the process in the invention and submit that the claim as amended renders the Examiner's rejection moot.

The Examiner also asserted that claims 62-104 are indefinite due to the use of the terms "high internal phase emulsion", "approaching", "predominantly extensional", and "type" are uncertain as to meaning and scope. Applicants respectfully traverse.

Applicants suggest that the term "high internal phase emulsion" is well known in the emulsion and surfactant art. Applicants wish to point out that, this term is quite well established in the literature and generally identifies an emulsion where the internal phase volume is greater than about 72%. See, for example, U.S. Patent Nos. 4,039,489 and 4,985,468, in which they both make reference to the following: "the study of high internal phase emulsions has been carried out for many years and the basic theory behind their preparation and structure has been discussed by K. J. Lissant in "Surfactant Science Series", Vol. 6, "Emulsion and Emulsion Technology", Part 1, edited by K. J. Lissant, Marcel Dekker Inc., New York, 1974." Both patents refer to emulsions where the internal phase volume is greater that 75%. See also PCT/US95/06897 for a discussion of high internal phase emulsion art.

With regard to the term "approaching", the term is commonly used in many arts to mean up to and including the value modified by the term. Examples of this language

can be seen in U.S. Patent No. 6,643,111 (claim 7) and U.S. Patent No. 6,659,965 (claim 7).

The term "predominantly extensional flows" is a well established term in the fluid and mixing arts, because all flows can be theoretically split into shear and extensional components. See U.S. Patent No. 6,354,729. Although pure shear flows can be obtained easily and maintained for indefinite length of time, "purely extensional" flows cannot be achieved easily and can not be maintained indefinitely. Therefore, although theoretically analyzed using computer codes, it is not possible to quantify the extensional components in batch mixers, but it is easier to qualitatively analyze certain types of flows, such as jet mixing or capillary entry/exit flows. Applicants refer to this in the text and that is why Applicants use multi point feed to reduce jet mixing which has a large extensional element.

Finally, the term "type" as used in the claims refers to the four basic types of pores disclosed in the specification at page 10, line 14 – page 12, line 19. Applicants respectfully submit that these terms are not indefinite and request withdrawal of the rejection.

The Examiner has rejected claim 63 because the Examiner states that it is unclear how claim 63 further limits claim 62. Further, the Examiner has rejected claims 64-69 and 72-74 as unclear where in the process of claim 62 the conditions of the claims are inserted into the process of claim 62.

The Examiner has rejected claim 75 stating that it is unclear how the process of claim 62 can produce the polymer scaffold of claim 75 since claim 62 does not have conditions to provide antecedent basis for a scaffold as required in claim 75. Claim 75 was further rejected for being unclear for failing to provide sufficient description of the polymer structure to be clear as to the structure required. The Examiner asserts that it is uncertain as to how one would know when discrete zones are present since the zones are not described sufficiently to know what constitutes a zone, as well as it is uncertain as to

what constitutes an internal phase of the polymer and how the pores and interconnects relate to each other to form a polymer structure.

Finally, the Examiner has rejected claims 76-93 because it is unclear how the conditions of the claims further modify the structure of claim 75. Applicants respectfully traverse.

Applicants have amended claim 75 to define features which are derived by the process of Claim 62, providing antecedent basis for the scaffold, and by defining zones by pore size. New Claim 104 is an independent claim which defines an alternative limitation of the scaffold of Claim 75, derived by the process of independent Claim 63, providing antecedent basis for the scaffold, and again defining zones by pore size. Support for both claims is discussed above. Claims 76 to 101 are amended to indicate how the conditions of the claims modify the structure of Claims 75 and 104, and the support for these amendments is also identified above.

Applicants submit that the rejected claims are not confusing and unclear. Claims 75-93 define a number of mechanisms differing in process variables which may be varied to alter the nature of a particular pore type (Basic) or to determine the presence or absence of an additional pore type, such as the Coalescence pore, Nano pore, and Microcapillary type.

With regard to the Examiner's statements about scaffolds, a scaffold may comprise (Claim 62) co-extruded zones of any two or more or Basic pores in low or high pore size, Coalescence pores and Nano pores. Alternatively (Claim 63) a scaffold may comprise any one or more zones, distinguished by providing Basic pores, coalesced pores which may be dispersed within non-coalesced Basic pores, and Nano-pores in the walls of the Basic pores and optionally in the walls of Coalescence pores together with a 3D network of Microcapillaries.

Applicants submit that the specification and original claims clearly recite the following:

a) Basic pores are created during the dosing of the emulsion and homogenizing of the emulsion, prior to polymerization;

b) Coalescence pores are also created during the homogenizing of the emulsion by adding substances in the aqueous or oil phase;

c) Microcapillaries pores are obtained after the emulsion and homogenization and prior to polymerization by inserting fibers into the HIPE emulsion and extracting or burning out after polymerization; and

d) Nano pores are created by adding filler in the oil phase during emulsion formation and solvent extracting after polymerization or by adding polymers in the emulsion which are soluble in the monomer, and optionally subsequently extracting.

Applicants submit that it would be apparent to one of ordinary skill in the art, where the conditions of claims 64 – 69 and 71 – 74 would be inserted in the process of claim 62 and 63 and where the conditions of claims 76 to 101 modify the structures of claims 75 and 104. Applicants have amended the claims only to clarify the subject matter of the invention. In view of the foregoing, Applicants respectfully request that all rejections regarding 35 U.S.C. § 112 be withdrawn.

<u>Rejection under 35 U.S.C. § 103(a)</u>

The Examiner rejected claims 62-101 under 35 U.S.C. § 103(a) as being unpatentable over Hough et al. (U.S. 5,071,747) (hereinafter, "Hough") in view of Shively et al. (WO 97/32612) (hereinafter, "Shively"). The Examiner stated that Hough discloses a process of making a scaffold as a support for cells by polymerizing monomers or pre-polymers in a continuous phase of an emulsion to obtain a scaffold having pores and interconnections. The Examiner also stated that Shively discloses obtaining

heterogeneous foams by polymerizing a high internal phase water-in-oil emulsion (HIPE). The Examiner has contended that it would have been obvious to use the HIPE to obtain the result of heterogeneous foam as disclosed by Shively having different regions with different properties or functions, and it would have been expected that such foam would be advantageous in Hough as a cell scaffold. The Examiner also contended that the conditions of the dependent claims for polymerization would have been obvious from conditions disclosed in Hough and Shively. The scaffold of Hough is used as a support for cells and combining the scaffold with the cells as in claims 94-101 would have been obvious. Applicants respectfully traverse.

To establish a *prima facie* case of obviousness, three basic criteria must be met. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art reference (or references when combined) must teach or suggest all the claim limitations. Moreover, the teaching or suggestion to make the claimed combination and the reasonable expectation of success must both be found in the prior art, not in applicant's disclosure. In re Vaeck, 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991).

Applicants respectfully point out that the combination of the teachings of Hough with Shively do not teach or suggest all the limitations of the claims as presently amended. It should be apparent to the Examiner that Hough fails to teach the formation of very large and very small Basic pores as defined in Claim 62 and 63, since Hough fails to teach the effects of mixing and temperature to obtain these. Hough simply uses electrolyte effect to control pore size and this is not sufficiently versatile to obtain the very large and very small Basic pores of the invention. Moreover, Hough fails to teach the formation of Coalescence and Nano pores and Microcapillaries.

Differences between Hough and Applicants' Invention

In the present invention, Applicants disclose and claim that the control of pore size and pore size distribution in PHP is achieved at the emulsification as well as polymerization stages, and control of pore size is also dependent on the chemical composition of the oil and aqueous phases. The interconnecting hole size is dependent on the polymerization conditions as well as the chemical composition of the oil and aqueous phases.

Applicants disclose that in order to obtain uniform pore size distribution, it is necessary to make sure that residence time distribution during emulsification is narrow. Emulsion droplet size decreases with increasing mixing time as well as mixing strength. Therefore, if the dosing of the internal phase is slow, residence time is broad and the droplets will have broad size distribution. Size distribution is narrowed if the mixing time is increased. However, increasing mixing time also decreases the droplet size therefore the control of the pore size becomes difficult especially when the pore size required is large.

Applicants have surprisingly found that the solution for narrow residence time distribution is to dose the internal phase as rapidly as possible. But this causes emulsion instability and the emulsion does not form. To prevent emulsion instability, the mixing strength is increased. Applicants discovered that there is a relationship between the dosing time and mixing speed in obtaining stable emulsion formation. For a given composition and mixing the dosing deformation rate R_E must be below a certain critical value for emulsion formation. This relationship and its application to the preparation of large pore size PHP are explained in the patent application (p. 21, 22). Hough, nor Shively teach or suggest this relationship.

Large pore size PHP is important in some applications including tissue engineering and biotechnology. Applicants discovered that, the pore size is best controlled by operating at high temperature above 60 C or more. This technique, coupled with low mixing rate operation, produces large pore size material in a re-producible

manner. Hough does not teach or suggest using temperatures above 60 C to control pore size.

Emulsion preparation is usually carried out using a batch mixing vessel. It is well known to experts in fluid mechanics every flow has shear and extensional flow components. The relative values of these two components are very difficult to quantify. It can be quantified in capillary flows exactly. At the exit or entry of a capillary, the extensional flow rate is ½ of the shear rate when the capillary exit/entrance is flat. Applicants found that extensional flows cause emulsion drop size reduction while the shear flows delay the size reduction. Applicants applied this principle to HIPE formation; in order to obtain small pore size HIPE the use of predominantly extensional flows and low temperatures (see temperature effect) are advocated. During the dosing of the internal phase, jetting of the liquid creates extensional flows and therefore our mixer was designed to prevent jetting and the flow was distributed from the bottom of the mixing vessel. We also used large impeller / vessel diameter ratio in order to enhance shear flow component. These points are explained in pages 19-21. Hough does not teach nor suggest the use of predominantly extensional flows and low temperatures to generate pores with sizes up to 0.5 μm.

Additionally, Applicants discovered (page 4) that very large and very small pore size PHP could not be obtained through the teaching of Hough. The effect of electrolyte on pore size was not so marked that it could solely be used to control pore size over a wide range, and in fact the upper limit was 50 μm.

Differences between Shively and Applicants' Invention

Shively teaches mixing, or bringing together in a layered manner, two or more different HIPEs with differing droplet size, to obtain multi-pore constructs. Alternatively, a single droplet size HIPE is prepared and while filling a container, the mixing conditions

are changed continuously in order to obtain varying droplet size HIPE. Subsequently, polymerization is carried out in order to obtain foams with multi-pore size.

Shively teaches two methods of layering:

a) Continuous extrusion of HIPE at different rates which creates polyhipe with a gradual change in structure and the control of the layering is difficult because extrusion at each condition must be predetermined and it depends on the size of the individual Polyhipe parts produced. Production of a sheet with several layers cannot be achieved so that desired size products could be cut off from such a sheet. Applicants submit that this technique cannot be used in the application disclosed and claimed in the present invention, let alone as a construct in tissue engineering;

b) Extrusion of two layers on top of each other creates a controlled structure in a sheet of material from where desired pieces can be cut. However, if the emulsion is not co-extruded, <u>as taught in the present invention</u>, the interface between two different layers will be weak and they can easily be separated. This is all the more important if the first layer is extruded into air and then the second layer is extruded onto the first layer, because the first layer exposed to air will yield closed pores and hence the interface will not only be weak but also will have closed pore structure. This follows the known technique of epitaxial polymerization given by one of the Applicants. See, G. Akay et al., Chem. Eng. Res. and Design, vol. 73, pp. 782-797 (1995). Layering will also entrap air at the interface and it will result in large defects. The technique of Shively cannot create concentric (cylindrical parts) layered structures either.

The Examiner has appreciated that Shively mentions regions of multiple-cells, in the context of closed cavities. Applicants point out that the claimed method and final product of the PHP in Applicants' invention are different than those of PCT WO 97/32612. Applicants obtain uniform but controlled pore size and interconnecting hole size, and achieve this through a combination of chemical composition, temperature and

flow conditions. In the present invention, when Applicants discuss regions of multiple-cells, the term "cells" refers to animal or bacteria cells, or micro-organisms. Shively fails to teach or suggest the creation of multi-pore constructs in this manner.

In addition, Shively also fails to teach or suggest the co-extrusion of HIPEs, as in the present invention, whereby two or more different HIPEs are brought together in a desired configuration to obtain a polyHIPE having zones as defined. It would not be possible to obtain the scaffold of the invention by the layering or continuous conditions change of Shively, because the interfaces would prevent barriers whereas in the extrusion method of the invention the interfaces provide continuity between adjacent and overlapping zones. Moreover certain structures require a shell in core structure, such as scaffolds resembling blood vessels and the like, whereby co-extrusion is superior to surrounding one cylindrical HIPE with a surrounding HIPE layer. Such structures are not taught or suggested in Shively.

Even if one of ordinary skill in the art was inspired to combine the teachings of Hough and Shively, and adapting for more effective interface formation by co-extrusion, they would simply obtain a scaffold comprising zones of different Basic pores of intermediate pore size, and there would be no teaching or suggestion of forming other pore types. The applications of such a scaffold would be very limiting, and nowhere in Shively or Hough is there taught or suggested a method of obtaining other pore types or HIPE configurations, and even less is there any teaching or suggestion of a method of obtaining larger and smaller pore types and capillary types, and even less so the methods for obtaining these. Accordingly, Applicants respectfully submit that one of ordinary skill in the art apprised with both Hough and Shively, even if he thought of combining the teaching of these very unrelated references, would not be able to derive the claimed methods or scaffolds of the present invention.

With regard to the dependant claims 94-101 add further elements to the claimed invention in terms of co-extrusion of HIPEs, methods for affecting emulsion properties by controlled dosing, temperature ranges of emulsion, use of fillers for further

functionality in the emulsion, functionality of microcapillaries for blood or nutrient supply, withdrawing expressed proteins and seeding of cells and the like, module configurations suited for organ formation, and uses of the scaffolds of the invention. None of the conditions or elements in these dependent claims are taught or even suggested in Hough or Shively.

Applicants submit that the Examiner has failed to establish a *prima facie* case of obviousness, because, as described in detail above, the Hough and Shively references when combined do not teach or suggest all the claim limitations of the present invention. Additionally, one of ordinary skill in the art would not have been motivated to combine the teaching of Hough and Shively to create the present invention. In view of the large number to technological differences between the prior art and the present invention described above, the Examiner has not put forth a sufficient basis for such motivation. As such, the Applicants respectfully request withdrawal of this rejection.

Applicant believes that all rejections have been properly overcome and the claims as amended are in condition for allowance.

If there are any questions, the Examiner is invited to call the attorney at 202-638-6666. Entry of the amendment and reconsideration is respectfully requested.

Respectfully submitted,

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